PATENT COOPERATION TREATY

From the
ERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001837	29.04.2004	30.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07F17/02

Applicant
THE UNIVERSITY COURT OF THE UNIVERSITY OF ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001837

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15

because:

☐ the said international application, or the said claims Nos. 15 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001837

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14,16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	5-11
	No:	Claims	1-4,12-14,16
Industrial applicability (IA)	Yes:	Claims	1-14,16
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/GB2004/001837

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims (Art. 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: Garcia et al., J. Organomet. Chem. 467 (1994), 119-126
D2: US A 2003/023088
D3: Aird et al., British Journal of Cancer 86 (2002), 1652-1657
D4: Morris et al., J. Med. Chem. 44(2001), 3616-3621

The present application relates to Ruthenium(II) complexes of the general formula (I) (claims 1-11), the compounds (I) for use in medicine (claim 12), the usage thereof for the preparation of a medicament (claim 13), pharmaceutical compositions thereof (claim 14), a method of treatment by administering the compounds (I) (claim 15) as well as a process for the preparation thereof (claim 16).

For the assessment of present claim 15 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The compounds IVa, IVb, Va and Vb according to D1 are representatives of the compounds (I), however excluded from the subject-matter of claim 1 by a proviso. D1 also

does not refer to an eventual use of the compounds disclosed therein as a medicine.

Ruthenium complexes which are structurally comparable to the compounds (I) according to the present case and which are also used as antineoplastic agents are known in the art, e.g. D2-D4.

The compounds (I) can be distinguished from the ruthenium(II) complexes as disclosed in D2 (cf. ex. 3-6,8-10), D3 (p. 1653, Fig. 1, 4th - 11th compound), D4 (cpds. 3-6, 8-10 of Table 1) insofar, as the bidentate ligand Y-L-Y' is different from the bidentate ligands used in the compounds of the prior art.

The subject-matter of claims 1-14 and 16 according to the present case is therefore novel in the sense of Article 33(2) PCT.

As closest prior art can be regarded D2.

The problem of the present application was to provide further ruthenium(II) complexes which are suitable for the treatment of tumors.

This problem has been solved by selected representatives of the compounds (I), as can be seen in the description.

Those compounds (I) which are a solution to the problem cannot be considered obvious for the man skilled in the art, as D1 does not disclose nor suggest diamine ligands the geometry of which is as rigid as those used in the present case (all the ligands employed in D1 are derivatives of ethylene diamine and thus have a much more flexible geometry).

In this respect the following is noted:

The Applicant is entitled to claim all obvious modifications of what was described (cf. Guidelines C-III, 6.2); alternative variations have to be supported by a certain number of examples (s. Guidelines C-II, 4.9); in this case the breadth of the main claim represents a reasonable generalisation of what has been exemplified, so that it can be assumed that every compound falling within its scope actually provides a solution to the problem underlying the invention.

It appears that - due to the extremely broad definition of Y-L-Y' - claim 1 includes a large variety of structural possibilities not yet explored by the applicant, i.e. compounds which are structurally so remote from those of the examples that their activity cannot be predicted within the limits of qualitative structure-activity-relationship considerations.

The applicant could - in order to overcome this objection - submit all information available to substantiate that all claimed compounds are an non-obvious solution to the problem underlying the application (cf. Article 33(3) PCT in conjunction with Articles 5 and 6 PCT) or, alternatively, restrict the claims concerned appropriately.

An inventive step in the sense of Article 33(3) PCT can therefore only be acknowledged for the subject-matter of claims 5-11.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.